SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Drug-Eluting Coronary Stent System
Device Trade Name:	PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™ and Over-The-Wire)
Device Procode:	NIQ
Applicant's Name and Address:	Boston Scientific Corporation One Scimed Place Maple Grove, MN 55311
Date of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P110010/S001
Date of FDA Notice of Approval:	June 1, 2012
Expedited:	Not Applicable

The original PMA (P110010) was approved on November 22, 2011 and is indicated for improving luminal diameter in patients with symptomatic heart disease or documented silent ischemia due to *de novo* lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 28 mm in length. The SSED to support the indication is available on the CDRH website and is incorporated by reference here: http://www.accessdata.fda.gov/cdrh_docs/pdf11/P110010b.pdf. The current supplement was submitted to expand the indication for the PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™ and Over-The-Wire).

II. INDICATIONS FOR USE

The PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System is indicated for improving luminal diameter in patients with symptomatic heart disease or documented silent ischemia due to *de novo* lesions in native coronary arteries ≥ 2.25 mm to ≤ 4.00 mm in diameter in lesions ≤ 34 mm in length.

III. CONTRAINDICATIONS

Use of the PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System is contraindicated in patients with known hypersensitivity to:

- 316L stainless steel or platinum
- everolimus or structurally-related compounds
- the polymers or their individual components (see details in Section V – Device Description)

Coronary Artery Stenting is contraindicated for use in:

- Patients who cannot receive recommended antiplatelet and/or anticoagulant therapy
- Patients judged to have a lesion that prevents complete inflation of an angioplasty balloon or proper placement of the stent or delivery device

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System Directions for Use (DFU).

V. DEVICE DESCRIPTION

The PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System is a device/drug combination product consisting of a drug/polymer-coated balloon-expandable stent, pre-mounted on a Monorail™ (MR) or Over-The-Wire (OTW) delivery catheter. The stent is made from a platinum chromium alloy (PtCr). The PROMUS Element™ Stent coating consists of two layers, a primer layer and a drug/polymer layer. The primer layer is composed of poly (n-butyl methacrylate) (PBMA). The drug/polymer coating consists of a polymer, PVDF-HFP, and the active pharmaceutical ingredient, everolimus. The PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System proposed in this supplement is identical to the Small Workhorse (SWH), Workhorse (WH) and Large Vessel (LV) models approved in P110010, with the exception of the stent length. The 32 mm and the 38 mm stent lengths have been added to the SWH, WH, and LV models. Please refer to the device description provided in the original SSED for additional details. The characteristics of the PROMUS Element™ Plus Stent System are described in **Table 1**.

Table 1: PROMUS Element™ Plus Stent System Product Description

	PROMUS Element™ Plus Monorail Stent Delivery System	PROMUS Element™ Plus Over-the-Wire Stent Delivery System
Available Stent Lengths (mm)	32, 28	
Available Stent Diameters (mm)	2.50, 2.75, 3.00, 3.50, 4.00	
Stent Material	Platinum Chromium Alloy (PtCr)	
Stent Strut Thickness	0.0032 inches (0.081 mm) for diameters 2.25 mm to 3.50 mm 0.0034 inches (0.086 mm) for diameter 4.00 mm	
Drug Product	A conformal coating of a polymer carrier loaded with 100 µg/cm² everolimus applied to the stent with a maximum nominal drug content of 177.3 µg on the largest stent (4.00 x 28 mm).	
Delivery System		
Effective Length	144 cm	
Delivery System Y-Adapter Ports	Single access port to inflation lumen. Guidewire exit port is located approximately 26 cm from tip. Designed for guidewire ≤ 0.014 inches (0.36 mm)	Y-Connector (Side arm for access to balloon inflation/deflation lumen. Straight arm is continuous with shaft inner lumen). Designed for guidewire ≤ 0.014 inches (0.36 mm)
Stent Delivery	A balloon, with two radiopaque balloon markers, nominally placed 0.4 mm (0.016 inches) beyond the stent at each end.	
Balloon Inflation Pressure	Nominal Inflation Pressure: • Diameters 2.25 mm, 2.50 mm, 2.75 mm, 3.00 mm, 3.50 mm, 4.00 mm: 11 atm (1117 kPa)	
	Rated Burst Inflation Pressure: • Diameters 2.25 mm – 2.75 mm: 18 atm (1827 kPa) • Diameters 3.00 mm – 4.00 mm: 16 atm (1620 kPa)	
Catheter Shaft Outer Diameter	2.3 F (≤ 0.80 mm) proximal and 2.7 F (≤ 0.95 mm) distal.	3.4F (≤ 1.20 mm) proximal for 2.25 to 4.00 mm sizes 2.4F (≤ 0.85 mm) distal for 2.25 to 2.75 mm sizes 2.7F (≤ 0.95 mm) distal for 3.00 to 4.00 mm sizes
Guide Catheter Minimum Inner Diameter Requirement	≥ 0.056 inches (1.42 mm)	≥ 0.066 inches (1.68 mm)

The device is available in the following diameters and lengths:

Table 2: PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail™ and Over-The-Wire)

			Stent Length							
			8 mm	12 mm	16 mm	20 mm	24 mm	28 mm	32 mm*	38 mm**
Balloon Diameter / Stent Model	SV	2.25 mm	X	X	X	X	X	X	X	N/A
	Designated Stent Model Separation									
	SWH	2.50 mm	X	X	X	X	X	X	LL	LL
		2.75 mm	X	X	X	X	X	X	LL	LL
	Designated Stent Model Separation									
	WH	3.00 mm	X	X	X	X	X	X	LL	LL
		3.50 mm	X	X	X	X	X	X	LL	LL
	Designated Stent Model Separation									
	LV	4.00 mm	X	X	X	X	X	X	LL	LL

"X" indicates previously approved in the original PMA
* With the exception of the 2.25 x 32 mm SV stent which was included in the scope of the Original PMA (P110010), the 32 mm models are part of the scope of this PMA supplement.
** With the exception of the 2.25 x 38 mm SV stent which is not available, the 38 mm models are part of the scope of this PMA supplement.

Each stent is coated with 100 μg/cm^2 of everolimus of per mm^2 stent surface area in a formulation of 1:4.9 (w/w) drug-to-polymer ratio. **Table 3** provides the nominal total loaded dose of everolimus per nominal stent length/diameter for stent sizes from both the Original PMA and this PMA Supplement. The added 32 mm and 38 mm length SWH, WH and LV stent models are indicated with grey shading.

Table 3: Nominal Total Loaded Dose of Everolimus (μg) per Nominal Stent Length and Diameter

Stent Model		Stent Length							
Design	**Diameter**	**8 mm**	**12 mm**	**16 mm**	**20 mm**	**24 mm**	**28 mm**	**32 mm**	**38 mm**
Total Loaded Dose Everolimus/ Stent (μg)	**SV**	38.2	57.3	72.7	91.8	107.2	126.3	145.5	N/A
	SWH	38.9	60.6	78.0	95.4	112.7	130.1	151.8	177.9
	WH	42.0	60.1	84.3	102.4	120.5	138.6	162.8	192.9
	LV	56.1	80.4	104.6	128.8	153.0	177.3	201.5	241.8

SV – Small Vessel (2.25 mm)
SWH – Small Workhorse (2.50 mm and 2.75 mm)
WH – Workhorse (3.00 mm and 3.50 mm)
LV – Large Vessel (4.00 mm)
N/A – size not available

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of coronary artery disease: exercise, diet, smoking cessation, drug therapy, percutaneous coronary interventions (such as angioplasty and placement of bare metal stents, coated stents, and other drug eluting stents), and coronary artery bypass graft surgery (CABG). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

VII. MARKETING HISTORY

As of October 31, 2011, the PROMUS Element™ Everolimus-Eluting Coronary Stent System was commercially available in the following countries:

Albania	Algeria	Andorra	Antigua/Barbuda
Argentina	Armenia	Aruba	Australia
Austria	Azerbaijan	Bahamas	Bahrain
Bangladesh	Barbados	Belgium	Belize
Belarus	Bermuda	Bolivia	Brazil
Brunei	Bulgaria	Chile	China
Colombia	Costa Rica	Croatia	Cyprus
Czech Republic	Denmark	Djibouti	Dominican Republic
Dutch Antilles	Ecuador	Egypt	El Salvador
Estonia	Finland	France	Georgia
Germany	Great Britain	Greece	Guatemala
Guyana	Haiti	Honduras	Hong Kong
Hungary	Iceland	India	Ireland
Indonesia	Israel	Iran	Iraq
Italy	Jamaica	Jordan	Kenya
Korea	Kuwait	Latvia	Lebanon
Libya	Liechtenstein	Lithuania	Luxembourg
Macedonia	Macau	Malaysia	Malta
Martinique	Mexico	Moldavia	Morocco
Nepal	Myanmar	Netherlands	New Zealand
Nicaragua	Norway	Oman	Pakistan
Palestinian Territory	Panama	Paraguay	Peru
Philippines	Poland	Portugal	Qatar
Romania	Russia	Saudi Arabia	Serbia
Singapore	Slovakia	Sri Lanka	Slovenia
South Africa	Spain	Surinam	Sweden
Switzerland	Syria	Taiwan	Thailand
Trinidad/Tobago	Tunisia	Turkey	Ukraine
United Arab Emirates	Uruguay	Venezuela	Vietnam
Yemen			

As of October 31, 2011, approximately 557,532 stents have been distributed outside the United States (OUS). No products have been withdrawn from the market in any country for any reason related to its safety or effectiveness.

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VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of a coronary stent in native coronary arteries:

- Abrupt stent closure
- Acute myocardial infarction
- Allergic reaction to anti-coagulant and/or antiplatelet therapy, contrast medium, or stent materials
- Angina
- Arrhythmias, including ventricular fibrillation and ventricular tachycardia
- Arteriovenous fistula
- Bleeding
- Cardiac tamponade
- Cardiogenic shock/pulmonary edema
- Coronary aneurysm
- Death
- Dissection
- Emboli, distal (air, tissue or thrombotic material or material from devices(s) used in the procedure)
- Heart failure
- Hematoma
- Hemorrhage, which may require transfusion
- Hypotension/hypertension
- Infection, local or systemic
- Ischemia, myocardial
- Pain, access site
- Perforation or rupture of coronary artery
- Pericardial effusion
- Pseudoaneurysm, femoral
- Renal insufficiency or failure
- Respiratory failure
- Restenosis of stented segment
- Stent embolization or migration
- Stent fracture
- Stent thrombosis/occlusion
- Stroke/cerebrovascular accident/transient ischemic attack
- Total occlusion of coronary artery
- Vessel spasm
- Vessel trauma requiring surgical repair or reintervention

Zortress®, the oral formulation of everolimus developed by Novartis Pharmaceuticals Corporation, has been evaluated in clinical trials and is approved in the United States for the prevention of organ rejection in adult kidney transplant recipients at the dose of 1.5

mg/day. Outside the U.S., Zortress® is sold under the brand name, Certican®, in more than 70 countries. Everolimus is also approved in the United States under the name of Afinitor ®for patients with advanced renal cell carcinoma (cancer), after failure of treatment with sunitinib or sorafenib, at doses of 5 to 20 mg/day when taken by mouth. The following list includes the known risks of everolimus at the oral doses listed above. The amount of drug that circulates in the bloodstream following implantation of a PROMUS Element™ stent is several folds lower than that obtained with oral doses (1.5 mg to 20 mg/day, see Section 7.2, Pharmacokinetics).

- Abdominal pain (including upper abdominal pain)
- Anemia
- Angioedema
- Anorexia
- Asthenia
- Constipation
- Cough
- Delayed wound healing/fluid accumulation
- Diarrhea
- Dyslipidemia (including hyperlipidemia and hypercholesterolemia)
- Dysgeusia
- Dyspepsia
- Dyspnea
- Dysuria
- Dry skin
- Edema (peripheral)
- Epistaxis
- Fatigue
- Headache
- Hematuria
- Hyperglycemia (may include new onset of diabetes)
- Hyperkalemia
- Hyperlipidemia
- Hypertension
- Hypokalemia
- Hypomagnesemia
- Hypophosphatemia
- Increased serum creatinine
- Infections and serious infections: bacterial, viral, fungal, and protozoal infections (may include herpes virus infection, polyoma virus infection which may be associated with BK virus associated nephropathy, and/or other opportunistic infections)
- Insomnia
- Interaction with strong inhibitors and inducers of CY3PA4
- Leukopenia
- Lymphoma and other malignancies (including skin cancer)

- Male infertility (azospermia and/or oligospermia)
- Mucosal inflammation (including oral ulceration and oral mucositis)
- Nausea
- Neutropenia
- Non-infectious pneumonitis
- Pain: extremity, incision site and procedural, back, chest, musculoskeletal
- Proteinuria
- Pruritus
- Pyrexia
- Rash
- Stomatitis
- Thrombocytopenia
- Thrombotic microangiopathy (TMA)/Thrombotic thrombocytopenic purpura (TTP)/Hemolytic uremic syndrome (HUS)
- Tremor
- Upper respiratory tract infection
- Urinary tract infection
- Vomiting

Live vaccines should be avoided and close contact with those that have had live vaccines should be avoided. Fetal harm can occur when administered to a pregnant woman. There may be other potential adverse events that are unforeseen at this time.

For the specific adverse events that occurred in the PLATINUM clinical studies, please see Section X – Summary of Primary Clinical Studies below.

IX. SUMMARY OF NONCLINICAL STUDIES

No new preclinical studies were submitted or required for the approval of the expanded indication proposed in this PMA Supplement. Please see the original SSED for details.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

The PLATINUM Clinical Program is evaluating the PROMUS Element™ Everolimus-Eluting Platinum Chromium Coronary Stent System for the treatment of *de novo* atherosclerotic lesions in 5 parallel studies. The Program includes the PLATINUM Trial, which comprises a workhorse (WH) randomized controlled trial (RCT) with single-arm small vessel (SV), long lesion (LL), and pharmacokinetics (PK) sub-studies, and the PLATINUM quantitative coronary angiography (QCA) study. Please refer to the original SSED for details on the WH, SV, PK, and QCA studies.

The LL sub-study was performed to establish a reasonable assurance of safety and effectiveness for the proposed expanded indications under IDE G080202. Data from this clinical sub-study were the basis for the PMA Supplement approval decision. A summary of the clinical study is presented below.

A. Study Design

Patients were treated between February 10, 2009 and March 4, 2010. The database for this PMA supplement reflected data collected through March 16, 2011 and included 102 patients at 30 investigational sites.

PLATINUM Long Lesion (LL) is a prospective, single-arm, multi-center sub-study of the PLATINUM Trial, which was designed to evaluate the safety and effectiveness of the PROMUS Element™ Everolimus-Eluting Platinum Chromium Coronary Stent System in the treatment of *de novo* coronary lesions. The sub-study compares outcomes in patients treated with the 32 mm or 38 mm PROMUS Element™ stent to a performance goal based on outcomes in patients treated with one planned 32 mm TAXUS Express stent from the TAXUS V *De Novo* Trial. The primary endpoint was 12-month target lesion failure (TLF), defined as any ischemia-driven revascularization of the target lesion (TLR), myocardial infarction (MI) (Q-wave and non–Q-wave) related to the target vessel, or cardiac death related to the target vessel.

An angiographic core lab was utilized for analysis of angiography data. A Clinical Events Committee (CEC) served as a multidisciplinary expert group responsible for the independent and ongoing adjudication of prespecified clinical events, including all reported deaths, MIs, target vessel revascularizations (TVRs), and stent thromboses (STs), as defined by the clinical protocol. A Data Monitoring Committee (DMC) of independent experts in cardiology, cardiovascular interventional therapy, and biostatistics worked to ensure patient safety by evaluating accumulating data from the PLATINUM Clinical Program.

Table 4: PLATINUM LL Sub-Study Trial Design

Purpose	Evaluation of safety and effectiveness in long lesions
Study Design	Prospective, single arm, multicenter, comparison to performance goal
Primary Endpoint	12M TLF
Number of Patients (ITT)	102 PROMUS Element
Polymer	PBMA, PVDF-HFP
Everolimus Dose Density	100 $\mu g/cm^2$
Lesion Criteria: Vessel Diameter (by visual estimate), mm	≥ 2.50 to ≤ 4.25
Lesion Criteria: Lesion Length (by visual estimate), mm	> 24 to ≤ 34
Total Target Lesions	1
Stent Matrix	2.50-4.00 mm diameter 32, 38 mm length
Post-Procedure Antiplatelet Therapy	Thienopyridine: at least 6 months, ideally for 12 months in patients not at high risk of bleeding; ASA: indefinitely
Follow-Up	Clinical: 30 days, 6 months, 1 year, 18 months, annually 2-5 years
Abbreviations: ASA=aspirin; ITT=intent-to-treat; LL = Long Lesion; PBMA=poly (n-butyl methacrylate); PVDF-HFP=poly (vinylidene fluoride-co-hexafluoropropylene); TLF=target lesion failure.	

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the PLATINUM LL sub-study was limited to patients who met the following inclusion criteria:

Clinical Inclusion Criteria	• Patient must be at least 18 years of age • Patient (or legal guardian) understands the study requirements and the treatment procedures and provides written informed consent before any study-specific tests or procedures are performed • For patients less than 20 years of age enrolled at a Japanese site, the patient and the patient's legal representative must provide written informed consent before any study-specific tests or procedures are performed • Patient is eligible for percutaneous coronary intervention (PCI) • Patient has documented stable angina pectoris or documented silent ischemia; or unstable angina pectoris • Patient is an acceptable candidate for coronary artery bypass grafting (CABG) • Patient has a left ventricular ejection fraction (LVEF) ≥ 30% as measured within 30 days prior to enrollment • Patient is willing to comply with all protocol-required follow-up evaluations
Angiographic Inclusion Criteria (visual estimate)	• Target lesion must be a de novo lesion located in a native coronary artery with a visually estimated reference vessel diameter (RVD) as follows: o ≥ 2.50 mm and ≤ 4.25 mm for the non-randomized LL subtrial (LL selection criteria) • Target lesion length must measure (by visual estimate) as follows. o > 24 mm and ≤ 34 mm for the non-randomized LL subtrial (LL selection criteria) • Target lesion must be in a major coronary artery or branch with visually estimated stenosis ≥ 50% and < 100% with Thrombolysis in Myocardial Infarction (TIMI) flow > 1

Patients were not permitted to enroll in the PLATINUM LL sub-study if they met any of the following exclusion criteria:

Clinical Exclusion Criteria	• Patient has clinical symptoms and/or electrocardiogram (ECG) changes consistent with acute MI • Patient has had a known diagnosis of recent MI (i.e., within 72 hours prior to the index procedure) and has elevated enzymes at the time of the index procedure as follows: o Patients are excluded if any of the following criteria are met at the time of the index procedure: o If CK-MB > 2× upper limit of normal (ULN), the patient is

	excluded regardless of the CK Total o If CK-MB is 1-2× ULN, the patient is excluded if the CK Total is > 2× ULN o If CK Total/CK-MB are not used and Troponin is, patients are excluded if the following criterion is met at the time of the index procedure. o Troponin > 1× ULN with at least one of the following: o Patient has ischemic symptoms and ECG changes indicative of ongoing ischemia (e.g., > 1 mm ST segment elevation or depression in consecutive leads or new left bundle branch block [LBBB]); o Development of pathological Q-waves in the ECG; or o Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality ***Note***: For patients with unstable angina or patients who have had a recent MI, CK Total/CK-MB (or Troponin if CK Total/CK-MB are not used) must be documented prior to enrolling/randomizing the patient • Patient has received an organ transplant or is on a waiting list for an organ transplant • Patient is receiving or scheduled to receive chemotherapy within 30 days before or after the index procedure • Patient is receiving oral or intravenous immunosuppressive therapy (i.e., inhaled steroids are not excluded) or has known life-limiting immunosuppressive or autoimmune disease (e.g., human immunodeficiency virus, systemic lupus erythematosus, but not including diabetes mellitus) • Patient is receiving chronic (≥ 72 hours) anticoagulation therapy (e.g., heparin, coumadin) for indications other than acute coronary syndrome • Patient has a platelet count < 100,000 cells/mm^3 or > 700,000 cells/mm^3 • Patient has a white blood cell (WBC) count < 3,000 cells/mm^3 • Patient has documented or suspected liver disease, including laboratory evidence of hepatitis • Patient is on dialysis or has known renal insufficiency (i.e., estimated creatinine clearance < 50 ml/min by the Cockcroft Gault formula: [(140-age)*lean body weight (in kg)]/[plasma creatinine (mg/dl)*72]) • Patient has a history of bleeding diathesis or coagulopathy or will refuse blood transfusions • Patient has had a cerebrovascular accident (CVA) or transient ischemic attack (TIA) within the past 6 months, or has any permanent neurologic defect that may cause non-compliance with the protocol • Target vessel(s) or side branch has been treated with any type of PCI (e.g., balloon angioplasty, stent, cutting balloon, atherectomy) within 12 months prior to the index procedure

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	• Target vessel(s) has been treated within 10 mm proximal or distal to the target lesion (by visual estimate) with any type of PCI (e.g., balloon angioplasty, stent, cutting balloon, atherectomy) at any time prior to the index procedure • Non-target vessel or side branch has been treated with any type of PCI (e.g., balloon angioplasty, stent, cutting balloon, atherectomy) within 24 hours prior to the index procedure • Planned or actual target vessel(s) treatment with an unapproved device, directional or rotational coronary atherectomy, laser, cutting balloon, or transluminal extraction catheter immediately prior to stent placement • Planned PCI or CABG after the index procedure • Patient previously treated at any time with coronary intravascular brachytherapy • Patient has a known allergy to the study stent system or protocol-required concomitant medications (e.g., stainless steel, platinum, cobalt, chromium, nickel, tungsten, acrylic, fluoropolymers, everolimus, thienopyridines, aspirin, contrast) that cannot be adequately premedicated • Patient has an active peptic ulcer or active gastrointestinal (GI) bleeding • Patient has one of the following. o Other serious medical illness (e.g., cancer, congestive heart failure) that may reduce life expectancy to less than 24 months o Current problems with substance abuse (e.g., alcohol, cocaine, heroin, etc.) o Planned procedure that may cause non-compliance with the protocol or confound data interpretation • Patient is participating in another investigational drug or device clinical trial that has not reached its primary endpoint • Patient intends to participate in another investigational drug or device clinical trial within 12 months after the index procedure • Patient with known intention to procreate within 12 months after the index procedure (Women of child-bearing potential who are sexually active must agree to use a reliable method of contraception from the time of screening through 12 months after the index procedure.) • Patient is a woman who is pregnant or nursing (A pregnancy test must be performed within 7 days prior to the index procedure in women of child-bearing potential.) • LL patient has more than 1 target lesion, or more than 1 target lesion and 1 non-target lesion, which will be treated during the index procedure
Angiographic Exclusion Criteria (visual estimate)	• Target lesion meets any of the following criteria: o Aorto-ostial location (i.e., lesion located within 5 mm of the ostium by visual estimate)

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	○ Left main location ○ Located within 5 mm of the origin of the left anterior descending (LAD) coronary artery or left circumflex (LCX) coronary artery by visual estimate ○ Located within a saphenous vein graft or an arterial graft ○ Will be accessed via a saphenous vein graft or an arterial graft ○ Involves a side branch ≥ 2.0 mm in diameter by visual estimate ○ Involves a clinically significant side branch < 2.0 mm in diameter by visual estimate that has a clinically significant stenosis at the ostium ○ TIMI flow 0 (total occlusion) or TIMI flow 1 prior to wire crossing ○ Excessive tortuosity proximal to or within the lesion ○ Extreme angulation proximal to or within the lesion ○ Target lesion and/or target vessel proximal to the target lesion is moderately to severely calcified by visual estimate ○ Restenotic from previous intervention ○ Thrombus, or possible thrombus, present in the target vessel • Non-target lesion to be treated during the index procedure meets any of the following criteria: ○ Located within the target vessel ○ Located within a bypass graft (venous or arterial) ○ Left main location ○ Chronic total occlusion ○ Involves a complex bifurcation (e.g., bifurcations requiring treatment with more than 1 stent) ○ Restenotic from previous intervention • Patient has unprotected left main coronary artery disease (> 50% diameter stenosis) • Patient has protected left main coronary artery disease and a target lesion in the LAD or LCX • Patient has an additional clinically significant lesion(s) in the target vessel for which an intervention within 12 months after the index procedure is likely to be required • Patient has 2 target lesions in the same vessel that are separated by less than 15 mm (by visual estimate) ***Note:*** Multiple focal stenoses will be considered as a single lesion if they can be completely covered with 1 stent.

2. Follow-up Schedule

After hospital discharge, all enrolled patients are scheduled to return for clinical follow-up examinations at 30 days, 6 months, 12 months, 18 months, 2 years, and annually to 5 years postoperatively. Starting with the 18-month visit, follow-up will be limited to the safety analysis set, which is composed of all study patients who received a PROMUS Element™ stent. Follow-up is complete through 1 year,

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the timing at which the primary endpoint for the trial was assessed, with additional follow-up ongoing. Regarding antiplatelet therapy, the protocol mandated compliance with 2007 ACC/AHA/SCAI Guidelines for PCI.[1]

Preoperatively, the following evaluations were performed, and data was obtained, in relation to the index procedure: Informed Consent; Confirmation of clinical eligibility criteria; Patient demographics; Physical assessment (including weight and height); General medical history (including angina status, diabetes mellitus status, and LVEF); Laboratory tests [serum creatinine, glycosylated hemoglobin (HbA_{1C}), CBC with platelets, pregnancy test (as needed)]; Metabolic Syndrome assessment (BP, HDL cholesterol, fasting glucose, fasting triglycerides, waist circumference); Assessment of cardiac medications; 12-lead ECG; Cardiac Enzymes (CK, and CK-MB and/or troponin); Previous PCI procedure information; Venous blood draw (for patients enrolled in the PK sub-study); Assessment/administration of current anti-thrombotic and anti-platelet medications; and Baseline angiographic assessment.

Postoperatively, the objective parameters measured during the study are outlined as follows: 12-lead ECG (discharge, 12-month visit); Cardiac Enzymes [CK, and CK-MB and/or troponin] (discharge); Serial venous blood draws [for patients enrolled in the PK sub-study] (discharge); Angina status; Assessment of anti-platelet medications; and Angiographic assessment(s) (as needed throughout follow-up period, per standard of care). Adverse events and complications were recorded at all visits.

3. Clinical Endpoints
    - Primary Safety and Effectiveness Composite Endpoint: 12-month Target Lesion Failure (TLF)
    - Additional Effectiveness Endpoints (in-hospital, 30 days, 6 months, 12 months, 18 months, 2-5 years):
        - Target Vessel Revascularization (TVR)
        - Target Lesion Revascularization (TLR)
        - TLF (primary endpoint at 12 months)
        - Target Vessel Failure (TVF): TVR, MI-related to the target vessel, or cardiac death related to the target vessel
    - Additional Safety Endpoints (in-hospital, 30 days, 6 months, 12 months, 18 months, 2-5 years):
        - Cardiac Death
        - Non-cardiac death
        - All-cause death
        - MI (Q-wave or non-Q-wave)
        - Cardiac death or MI
        - All death or MI
        - All death/MI/TVR
        - Stent thrombosis (definite or probably by Academic Research Consortium definitions)

Baseline, procedural, and follow-up data were summarized using descriptive statistics for continuous variables and frequency tables or proportions for discrete variables. Clinical and success/failure event rates are presented below as proportions with 95% confidence intervals. Continuous data are summarized by means, standard deviations, sample sizes, minimums, and maximums; 95% confidence intervals of the means are provided. All analyses of primary and additional endpoints were based on patients with sufficient follow-up. Endpoints were analyzed using 2 populations: intent-to-treat (ITT) (N=102) and per-protocol (N=100, includes only patients who received a study stent). The primary analyses were by per-protocol.

The rate of the primary endpoint, TLF at 12 months, was compared to a predefined performance goal (PG) of 19.4% based on historical TAXUS Express results. The PG equals the historical TAXUS Express Long Lesion 12-month TLF rate of 16.9% plus a 2.5% delta. The historical TAXUS Express Long Lesion rate is the rate of 12-month TLF for patients in the TAXUS V *De Novo* Trial with one planned TAXUS Express 32 mm stent, adjusted for oculostenotic reflex due to protocol-mandated angiographic follow-up, which was not required in the PLATINUM trial. A one-group exact binomial test was used to test the hypothesis that the primary endpoint rate in the PROMUS Element™ cohort is less than the PG.

B. Accountability of PMA Cohort

At the time of database lock, of the 102 patients included in the intent-to-treat analysis set, a total of 96 patients (94.1%) were evaluable for the 12-month primary endpoint. Patient disposition for the ITT analysis set is shown in **Table 5**.

Table 5: PLATINUM Long Lesion Patient Disposition, ITT, All Patients (N=102)

Category	PROMUS Element Stent
ITT Analysis Set	102
Death ≤ 395 days, no 12-month clinical follow-up performed	1
Eligible for 12-month clinical follow-up[a]	101
12-month clinical follow-up performed[b]	94.1% (95/101)
Office visit	86
Telephone contact	9
No 12-month clinical follow-up performed	6
Prematurely discontinued	1
Death > 395 days	0
Withdrew consent	1
Lost to follow-up	0
Adverse event	0
Investigator discretion	0

Transplant or removal of target organ	0
Other	0
Missed 12-month visit	5
With later follow-up visit performed	1
No later follow-up visit performed	4
12-month clinical follow-up or death[c]	94.1% (96/102)
12-month clinical follow-up patient accountability[d]	93.1% (95/102)

Numbers are counts of patients or % (count/sample size).

a: Patients who died prior to completion of follow-up window and prior to completing a 12-month clinical follow-up visit are considered censored and are excluded from calculation of proportion of patients who completed clinical follow-up visit.

b: Based on patients eligible for 12-month clinical follow-up

c: Includes patients who have died in both the numerator and the denominator; based on the ITT analysis set

d: All patients with 12-month follow-up out of all ITT patients

Abbreviations: ITT=intent-to-treat; LL=long lesion

C. Study Population Demographics and Baseline Parameters

Table 6 presents baseline demographic and clinical characteristics for the ITT analysis set (N=102). Average age was 65.9 ± 9.8. Approximately 63% of patients were male, and 30% of patients were medically treated diabetics.

Table 6: PLATINUM Long Lesion Baseline Demographics and Clinical Characteristics, ITT Analysis Set (N=102)

Parameter	PROMUS Element Stent (N=102)
Male	62.7% (64/102)
Age (years)	65.94±9.79 (102) (42.00, 90.00)
General Medical History	
Smoking, ever	64.0% (64/100)
Current	17.0% (17/100)
Previous	47.0% (47/100)
Diabetes (medically treated)	30.0% (30/100)
Insulin	9.0% (9/100)
Oral medications (no insulin)	21.0% (21/100)
Diabetes treated with diet only	2.0% (2/100)
Hyperlipidemia (medically treated)	82.4% (84/102)
Hypertension (medically treated)	82.4% (84/102)
History of bleeding disorder	1.0% (1/102)
Gastrointestinal	1.0% (1/102)
Hematologic dyscrasia	0.0% (0/102)
Cardiac History	
Angina, stable	56.4% (57/101)
Angina, unstable	23.8% (24/101)
Angina, none	19.8% (20/101)

Table 6: PLATINUM Long Lesion Baseline Demographics and Clinical Characteristics, ITT Analysis Set (N=102)

Parameter	PROMUS Element Stent (N=102)
Silent ischemia	22.0% (22/100)
Family history of coronary artery disease	50.5% (49/97)
Previous myocardial infarction	33.3% (34/102)
History of congestive heart failure	2.9% (3/102)
Previous percutaneous coronary intervention	38.2% (39/102)
Previous coronary artery bypass graft	11.8% (12/102)
History of arrhythmia	13.7% (14/102)
Left ventricular ejection fraction (%)	59.09±11.05 (101) (34.00, 85.00)
Not measured or not known	1.0% (1/102)
History of multivessel disease	47.1% (48/102)
History of left main disease	3.0% (3/101)
Neurologic, Renal, and Peripheral History	
History of TIA or CVA	11.8% (12/102)
Transient ischemic attack (TIA)	4.9% (5/102)
Cerebrovascular accident (CVA)	6.9% (7/102)
History of renal disease	6.9% (7/102)
History of peripheral vascular disease	8.9% (9/101)

Numbers are presented as mean±standard deviation (n) or % (count/sample size).
Abbreviations: CVA=cerebrovascular accident; ITT=intent-to-treat; TIA=transient ischemic attack

Table 7 presents baseline lesion characteristics for the ITT population as determined by core lab QCA and as reported by clinical sites. By QCA, mean reference vessel diameter (RVD) was 2.56 ± 0.40 mm. Average lesion length was 24.38 ± 8.21 mm. Diameter stenosis was approximately 72%, and approximately 97% of treated lesions were type B2/C.

Table 7: PLATINUM Long Lesion Baseline Lesion Characteristics, ITT Analysis Set (N=102)

Parameter	PROMUS Element Stent (N=102)
Quantitative Coronary Angiography Analyses	
Target lesion vessel	
Left anterior descending artery	43.1% (44/102)
Left circumflex artery	21.6% (22/102)
Right coronary artery	35.3% (36/102)
Left main coronary artery	0.0% (0/102)
Lesion location	
Proximal	47.1% (48/102)
Mid	42.2% (43/102)
Distal	5.9% (6/102)
Ostial	4.9% (5/102)
Reference vessel diameter (mm)	2.56±0.40 (102) (1.79, 3.72)
Minimum lumen diameter (mm)	0.73±0.30 (102) (0.00, 1.61)
Percent diameter stenosis	71.70±10.96 (102) (28.04, 100.00)
Lesion length (mm)	24.38±8.21 (102) (5.77, 52.87)
Eccentric lesion	59.8% (61/102)
Bend (degrees)	36.08±19.60 (102) (10.00, 120.00)
Thrombus	0.0% (0/102)
Tortuosity, any	4.9% (5/102)
Moderate	3.9% (4/102)
Severe	1.0% (1/102)
Calcification, any	36.3% (37/102)
Moderate	28.4% (29/102)
Severe	7.8% (8/102)
Ulcer	9.8% (10/102)
Aneurysm	2.0% (2/102)
Total occlusion	2.0% (2/102)

Table 7: PLATINUM Long Lesion Baseline Lesion Characteristics, ITT Analysis Set (N=102)

Parameter	PROMUS Element Stent (N=102)
Branch vessel disease	13.7% (14/102)
Side branch stenosis (%)	67.50±8.93 (14) (60.00, 85.00)
Lesion type (modified ACC/AHA)	
A	1.0% (1/102)
B1	2.0% (2/102)
B2	20.6% (21/102)
C	76.5% (78/102)
B2/C	97.1% (99/102)
Preprocedure TIMI flow	
0	2.0% (2/102)
1	0.0% (0/102)
2	3.9% (4/102)
3	94.1% (96/102)
Site Reported Lesion Characteristics	
Lesion length (mm)	29.76±2.96 (102) (24.50, 34.00)
Reference vessel diameter (mm)	2.87±0.34 (102) (2.50, 3.75)
Percent diameter stenosis (%)	82.42±8.91 (102) (60.00, 99.00)

Numbers are presented as mean±standard deviation (n) (mininum, maxinum) or % (count/sample size).
Abbreviation: ACC/AHA=American College of Cardiology/American Heart Association; ITT=intent-to-treat; TIMI=Thrombolysis In Myocardial Infarction

D. Safety and Effectiveness Results

1. Primary Safety and Effectiveness Endpoint

The primary endpoint of the trial was met and is reported in **Table 8**. The rate of 12-Month TLF was shown to be significantly less than the performance goal.

Table 8: PLATINUM Long Lesion Primary Endpoint

Per Protocol Patients[1]	PROMUS Element Stent (N=100)	[95% CI]	One-sided 95% UCB[2]	Performance Goal	P Value[3]
12-Month TLF	3.2% (3/95)	[0.7%, 9.0%]	7.96%	19.4%	<0.0001

Intent-to-Treat Patients	PROMUS Element Stent (N=102)	[95% CI]	One-sided 95% UCB[2]	Performance Goal	P Value[3]
12-Month TLF	3.1% (3/96)	[0.6%, 8.9%]	7.88%	19.4%	<0.0001

[1] Primary analysis for comparing to the performance goal and study success criterion.

[2] UCB is the Clopper-Pearson upper confidence bound.

[3] *P* values are one-sided from the exact binomial test.

12-Month TLF is the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Adverse effects that occurred in the PMA clinical study:

Site-reported serious adverse events through 12 months post index procedure are summarized by Systems Organ Class (SOC) in **Table 9**.

Table 9: PLATINUM Long Lesion Site-Reported Serious Adverse Events to 365 Days, ITT, All Patients (N=102)

Serious Adverse Event	PROMUS Element Stent (N=102)	
Medical Dictionary for Regulatory Activities (MedDRA) System/Organ Class	**Events**	**Rate of Patients with Event**
Total	71	33.3% (34/102)
Cardiac disorders	23	15.7% (16/102)
General disorders and administration site conditions	10	8.8% (9/102)
Infections and infestations	8	5.9% (6/102)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6	3.9% (4/102)
Blood and lymphatic system disorders	5	3.9% (4/102)
Nervous system disorders	3	2.9% (3/102)
Vascular disorders	3	2.0% (2/102)
Investigations	2	2.0% (2/102)
Metabolism and nutrition disorders	2	2.0% (2/102)
Renal and urinary disorders	2	2.0% (2/102)
Respiratory, thoracic and mediastinal disorders	2	2.0% (2/102)
Skin and subcutaneous tissue disorders	2	2.0% (2/102)
Eye disorders	1	1.0% (1/102)
Injury, poisoning and procedural complications	1	1.0% (1/102)
Reproductive system and breast disorders	1	1.0% (1/102)

"Events" numbers are total episodes of each type of event among all patients.

"Rate of Patients with Event" numbers are percent of patients who experienced one or more episodes of the event.

"Events" numbers for "TOTAL" are the sum of the individual event category totals.

"Rate of Patients with Event" numbers for "TOTAL" is the percent of patients who experienced an adverse event.

2. Secondary Endpoints

Post-procedure angiographic outcomes are shown in **Table 10** and rates for all death, cardiac death, MI, revascularization, and stent thrombosis are shown in **Table 11** and **Table 12**.

Table 10: PLATINUM Long Lesion Post-Procedure Angiographic Results

Angiographic Outcomes	**PROMUS Element Stent (N=102)**
MLD (mm), In-stent	2.39±0.32 (102)
MLD (mm), Analysis Segment	2.08±0.37 (102)
Acute Gain (mm), In-stent	1.66±0.36 (102)
Acute Gain (mm), Analysis Segment	1.35±0.40 (102)
% DS, In-stent	6.82±9.46 (102)
% DS, Analysis Segment	19.50±7.66 (102)
Abbreviations: DS=diameter stenosis; MLD=minimum lumen diameter	

Table 11: PLATINUM Long Lesion 12-Month Clinical Results, ITT, All Patients

	PROMUS Element Stent (N=102)
EFFECTIVENESS	
TVR, Overall	4.1% (4/97)
TLR, Overall	3.1% (3/97)
TLR, PCI	3.1% (3/97)
TLR, CABG	0.0% (0/97)
Non-TLR, Overall	2.1% (2/97)
Non-TLR, PCI	2.1% (2/97)
Non-TLR, CABG	0.0% (0/97)
TLF	3.1% (3/96)
SAFETY	
Total Death	1.0% (1/97)
Cardiac Death or MI	0.0% (0/97)
Cardiac Death	0.0% (0/97)
MI	0.0% (0/97)
Q-wave MI	0.0% (0/97)
Non-Q-wave MI	0.0% (0/97)
ARC Stent Thrombosis	
Definite or Probable	0.0% (0/96)
Definite	0.0% (0/96)
Probable	0.0% (0/96)

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

Numbers are % (count/sample size)

Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass graft; ITT=intent-to-treat; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLF=target lesion failure; TLR=target lesion revascularization; TVR=target vessel revascularization

Table 12: PLATINUM Long Lesion ARC Definite and Probable Stent Thrombosis, ITT Patients

Intent-to-Treat Patients	PROMUS Element Stent (N=102)
ARC Definite & Probable Stent Thrombosis[1]	
Cumulative through 1 year	0.0% (0/96)
Acute ST (≤ 24 hrs)	0.0% (0/102)
Subacute ST (> 24 hrs and ≤ 30 days)	0.0% (0/102)
Late ST (> 30 days and ≤ 12 months)	0.0% (0/101)

To be included in the calculation of stent thrombosis (ST) rate for a given interval, a patient either had to have a stent thrombosis during the interval (e.g. 31-365 days inclusive) or they had to be stent thrombosis-free during the interval with last follow-up on or after the first day of the given interval (e.g. 31 days).

[1] Academic Research Consortium (ARC) stent thrombosis is defined as follows.[2]

1. Definite ST is considered to have occurred after intracoronary stenting by either angiographic or pathologic confirmation of stent thrombosis.
2. Probable ST is considered to have occurred after intracoronary stenting in the following cases:
   Any unexplained death within the first 30 days following stent implantation.
   Irrespective of the time after the index procedure, any MI which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.

Numbers are % (Count/Sample Size).

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

Abbreviations: MI=myocardial infarction; ST=stent thrombosis

3. Subgroup Analyses

The PLATINUM LL trial data were retrospectively evaluated for possible sex-based differences in baseline characteristics and clinical outcomes, as well as for any interaction between treatment and sex/gender. The PLATINUM LL trial was not designed or powered to study safety or effectiveness in sex-specific subgroups, so these analyses were performed *post hoc* and are considered hypothesis generating.

In the PLATINUM LL ITT population, of the 102 patients enrolled, 64 patients were male (62.7%) and 38 patients were female (37.3%). In patients treated with the PROMUS Element stent, the 12-Month rate of TLF was 3.3% in males and 2.8% in females (**Table 13**). Given the small number of patients enrolled, no conclusions can be drawn from these data.

Table 13: PLATINUM Long Lesion Primary Endpoint Results by Gender, Intent-to-Treat, All Patients (N=102)			
	PROMUS Element Stent Male Patients (N=64)	**PROMUS Element Stent Female Patients (N=38)**	**Difference**
12-Month TLF	3.3% (2/60)	2.8% (1/36)	0.5%

This trial was not sized to determine the rate of low frequency events with a pre-specified precision.

Numbers are % (Count/Sample Size)

12-Month TLF is the proportion of patients who experience a target lesion failure (defined as any ischemia-driven revascularization of the target lesion [TLR], MI [Q-wave and non–Q-wave] related to the target vessel, or cardiac death related to the target vessel) up to 365 days post-procedure out of the population that have been followed for at least 335 days or who have experienced a TLF up to 365 days post-procedure.

Table 14 shows PLATINUM LL 12-month clinical results for male and female patients. Given the small number of patients enrolled, no conclusions can be drawn from these data.

Table 14: PLATINUM Long Lesion 12-Month Clinical Endpoints by Gender, Intent-to-Treat, PROMUS Element Male and Female Patients (N=102)		
	PROMUS Element Stent Male Patients (N=64)	**PROMUS Element Stent Female Patients (N=38)**
EFFECTIVENESS		
TVR, Overall	5.0% (3/60)	2.7% (1/37)
TLR, Overall	3.3% (2/60)	2.7% (1/37)
TLR, PCI	3.3% (2/60)	2.7% (1/37)
TLR, CABG	0.0% (0/60)	0.0% (0/37)
Non-TLR, Overall	1.7% (1/60)	2.7% (1/37)
Non-TLR, PCI	1.7% (1/60)	2.7% (1/37)
Non-TLR, CABG	0.0% (0/60)	0.0% (0/37)
TLF	3.3% (2/60)	2.8% (1/36)
SAFETY		
Total Death	0.0% (0/60)	2.7% (1/37)
Cardiac Death or MI	0.0% (0/60)	0.0% (0/37)
Cardiac Death	0.0% (0/60)	0.0% (0/37)
MI	0.0% (0/60)	0.0% (0/37)
Q-wave MI	0.0% (0/60)	0.0% (0/37)
Non-Q-wave MI	0.0% (0/60)	0.0% (0/37)
ARC Stent Thrombosis		
Definite or Probable	0.0% (0/60)	0.0% (0/36)
Definite	0.0% (0/60)	0.0% (0/36)
Probable	0.0% (0/60)	0.0% (0/36)

Table 14: PLATINUM Long Lesion 12-Month Clinical Endpoints by Gender, Intent-to-Treat, PROMUS Element Male and Female Patients (N=102)		
	PROMUS Element Stent Male Patients (N=64)	**PROMUS Element Stent Female Patients (N=38)**
This trial was not sized to determine the rate of low frequency events with a pre-specified precision. Numbers are % (Count/Sample Size) Abbreviations: ARC=Academic Research Consortium; CABG=coronary artery bypass grafting; MI=myocardial infarction; PCI=percutaneous coronary intervention; TLF=target lesion failure; TLR=target lesion revascularization; TVR=target vessel revascularization.		

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Circulatory System Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XII. CONCLUSIONS DRAWN FROM CLINICAL AND NON-CLINICAL STUDIES

The safety and effectiveness of the PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-The-Wire) are based on the results obtained from the following measures: biocompatibility; *in vivo* pharmacokinetics; *in vitro* engineering testing; coating characterization; chemistry, manufacturing and controls information; *in vivo* animal testing; sterilization; stability testing; and clinical studies. These tests revealed the following information:

A. Effectiveness Conclusions

The results of the PROMUS Element™ Long Lesion showed that the TLF rate at 12 months met the performance goal based on TAXUS Express 32 mm Stent results from the TAXUS V *De Novo* trial. The composite endpoint of TLF is comprised of both safety and effectiveness terms, however, the effectiveness term (TLR) is the primary contributor to TLF. Although TLR rate at 12 months was not a powered comparison in this study, TLR rate was favorable from a numerical standpoint.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in a clinical study conducted to support PMA Supplement approval as described above. The conclusions based on the nonclinical findings were previously described for the Original PMA.

The adverse effects of the device are based on data collected in a clinical study conducted to support PMA supplement approval as described above. The PLATINUM LL sub-study showed that in patients with symptomatic heart disease or documented silent ischemia due to *de novo* lesions in native coronary arteries, the adverse event rates for the PROMUS Element™ Long Lesion stents were clinically acceptable. Given the available supportive nonclinical and clinical data regarding the LL stent sizes provided in both the Original PMA and this PMA Supplement, the safety decision based on the PLATINUM LL sub-study was considered acceptable.

C. Benefit-Risk Conclusions

The probable benefits of the device are also based on data collected in a clinical study conducted to support PMA Supplement approval as described above. PROMUS Element Plus has been shown to be beneficial for improving luminal diameter in patients with symptomatic coronary artery disease or silent ischemia. Rates of target lesion failure (TLF) (defined as cardiac death related to the target vessel, MI related to the target vessel or target lesion revascularization) are non-inferior with PROMUS Element Plus in comparison to the TAXUS Express 32 mm drug-eluting stent.

Additional factors were considered in determining probable risks and benefits for the PROMUS Element™ Plus Everolimus-Eluting Platinum Chromium Coronary Stent System (Monorail and Over-The-Wire) device. Although the key clinical data supporting the safety and effectiveness of the 2.50 - 4.00 mm diameter stents that are $\leq$ 28 mm in length were obtained from a large, randomized controlled trial, the key clinical data supporting the safety and effectiveness of PROMUS Element Plus stents that are $\geq$ 32 mm in length were obtained from a single-arm, non-randomized study where the effectiveness outcome (TLF) was compared to a historical control. Important markers of safety, including death, MI, and stent thrombosis were low or not observed. Alternative treatments for coronary artery disease, including other coronary stents and both medical and surgical therapy, are available and the risks and benefits of these therapies were carefully considered. The risks and benefits of the PROMUS Element Plus were found to be similar to the risks and benefits of other approved drug-eluting stents.

In conclusion, given the available information above, the data support that for improving luminal diameter in patients with symptomatic heart disease or documented silent ischemia due to de novo lesions in native coronary arteries $\geq$ 2.25 mm to $\leq$ 4.00 mm in diameter in lesions $\leq$ 34 mm in length, the probable benefits outweigh the probable risks, and adds to the treatment options available to patients with symptomatic coronary artery disease and long coronary lesions.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use.

XIII. CDRH DECISIONS

CDRH issued an approval order on June 1, 2012. The final conditions of approval cited in the approval order are described below.

1. *Platinum Post-approval Study*: The applicant must incorporate the PROMUS Element Plus Everolimus-Eluting Platinum Chromium Coronary Stent System for stent lengths 32 and 38 mm (2.5 to 4 mm diameters) into the existing post-approval study required for P110010. This is a prospective, open-label, multi-center post-approval study, consisting of consecutively newly enrolled US patients with a follow-up duration of at least 5 years. The primary study objective is to evaluate cardiac death or myocardial infarction at 12 months. The secondary study objectives are to assess stent thrombosis at 5 years and the rate of longitudinal stent deformation. Both primary and secondary endpoints should be evaluated separately for the following categories: (1) lesion length $\leq$ 28 mm (diameter $\geq$ 2.25 mm and < 2.5 mm), (2) lesion length $\leq$ 24 mm (diameter $\geq$ 2.5 mm and $\leq$ 4.25 mm), and (3) lesion length > 24 mm and $\leq$ 34 mm (diameter $\geq$ 2.50 mm and $\leq$ 4.25 mm), as subset analyses. As part of the 2,689 patients needed for enrollment in the ongoing PAS, the applicant is required to follow a minimum of 200 patients through 5 years for the study objectives with PROMUS stent lengths 32 and 38 mm (2.5 to 4 mm diameters).

2. *Continued Follow-up of Premarket Cohort:* The study must be conducted as per protocol submitted in G080202 and the Post-Approval Study Analysis Protocol agreed upon on May 17, 2012 (via email). The study will consist of continued follow-up of the single-arm, multicenter, premarket cohort treated with PROMUS Element stents with lengths of 32 mm or 38 mm. The following endpoints will be examined at 18 months, 2-years, then annually through 5 years: target lesion revascularization, target lesion failure, target vessel revascularization (TVR), target vessel failure, MI (Q-wave and non–Q-wave), cardiac death, non-cardiac death, all death, cardiac death or MI, all death or MI, all death/MI/TVR and stent thrombosis (definite or probable by ARC definitions).

   The study population will consist of 100 adult IDE subjects treated with PROMUS Element Everolimus-Eluting Platinum Chromium Coronary Stent.

3. The issue of the optimal duration of dual antiplatelet therapy following PCI with drug eluting stents (DES) remains a critical question that is currently being studied in the DAPT trial. FDA acknowledges that the applicant is participating in this trial to address a condition of approval for the TAXUS Liberté DES (P060008). Patients treated with the PROMUS DES (approved as XIENCE V/PROMUS P070015) are also included in this trial. As the duration of dual antiplatelet therapy is also relevant for the PROMUS Element Plus, the applicant must fulfill the commitment to the condition of PMA approval for P060008. When appropriate, or as requested by FDA, the applicant should submit PMA supplements to the PROMUS Element Plus PMA (P110010) requesting approval to update the directions for use (DFU) to include the data collected in the overall DAPT trial. If the applicant does not fulfill the condition of approval for P060008, they must conduct or participate in a separate clinical trial that will develop

data to study the duration of dual antiplatelet therapy following implantation of the PROMUS Element Plus DES. When appropriate, or as requested by FDA, the applicant should submit PMA supplements to this PMA requesting approval to include these data in a DFU update.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

1. King SB, 3rd, Smith SC, Jr., Hirshfeld JW, Jr., et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines: 2007 Writing Group to Review New Evidence and Update the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention, Writing on Behalf of the 2005 Writing Committee. Circulation 2008;117:261-95.

2. Cutlip DE, Windecker S, Mehran R, et al. Clinical End Points in Coronary Stent Trials: A Case for Standardized Definitions. Circulation. 2007;115:2344-2351.